

Nonsmoker COPD: Is it a reality?

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines over the last few years have stopped emphasizing the categorization of chronic obstructive pulmonary disease (COPD) into emphysema or chronic bronchitis.^[1] This happened as a result of the fact that we do not find isolated pure emphysema or a pure chronic bronchitis, clinical COPD is always a mixture of these two entities. That is an example of the evolution of COPD based on available evidence. On the other hand, we are going to have new phenotype nonsmoker COPD. Nonsmoker COPD still remains inadequately covered in GOLD COPD guidelines. The etiology, pathophysiology, clinical presentation, and prognosis may significantly differ in nonsmoker COPD. Therefore, there is need to address this group of COPD more clearly.

The traditional COPD research includes GOLD-defined COPD and exclusion of parameters that do not fit in this frame. Over the years, there has been the growth of more and scientific evidence on approach and management of COPD.^[2] COPD is mainly attributed to a smoking-related accelerated decline in lung function mainly the forced expiratory volume in 1 s (FEV1). However, recent reports have clearly shown that usual decline in lung function in people having low initial FEV1 may also lead to COPD.^[3] It may also mean that people having lung damage due to underlying lung disease of varying etiologies may also develop lung function defects definable as COPD.

Recent research has also focused on different phenotypes of COPD. A COPD phenotype is defined as “a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes (symptoms, exacerbations, response to therapy, rate of disease progression, or death).”^[4] COPD may be considered to exist in a variety of phenotypic subgroups and the basis of characterization ranging from demographic factors such as age, gender, obesity to clinical characteristics, and comorbidities of COPD.^[5-7]

Although certain distinct COPD phenotypes have been identified over the years such as asthma-COPD overlap syndrome, frequent exacerbators, classic emphysema, and chronic bronchitis, the research so far in this field has been unconvincing. There is no clear consensus on what would be the best approach to diagnose and manage these individual phenotypes. This is mainly due to great heterogeneity of COPD, and for the sake of clarity, we will not emphasize the term “phenotypes” further here.

According to Augusti, as far as disease characterization of COPD is concerned, we are moving from characterization by FEV1 towards personalized medicine of COPD. It is likely that the concept of COPD phenotypes is likely to be abandoned in future.^[8]

In our opinion, to have a comprehensive approach aimed at performing current research and management, COPD should be grouped into two broad groups. One is classic COPD caused by smoking as the main etiological factor. Other is nonsmoker COPD which may be related to biomass fuel, diesel smoke, tuberculosis, silicosis, and others etiologies of COPD where small airways, alveoli are affected as a consequence of significant damage to lung due to a variety of disease processes. This group is more likely to be seen outside the western world. Studies suggest that these patients may behave differently than classic COPD.^[9] Some of these diseases may present as restriction in combination with obstruction on lung function tests. Although there may be some overlap, this distinction will help in planning specific research and formulating specific management strategies for this group of patients.

Nonsmoker COPD simply means that there is no exposure to tobacco smoke. This does not mean that a person is not exposed to any other form of environmental pollutants or an endogenous ailment. The biomass fuel exposure is one of the main indoor air pollutant studied in this group of patients. In an interesting study conducted by Mohan *et al.* serum matrix, metalloproteinase-9 and tissue inhibitor of metalloproteinases-1 in COPD due to tobacco smoking were compared with COPD in nonsmokers having exposure to biomass-related indoor air pollution.^[10] It was found that protease-antiprotease balance in COPD was similar in tobacco exposure and biomass exposure but was different than the controls.

Large population-based studies are available documenting incidence and prevalence of nonsmoker COPD. In Copenhagen city heart study, 8045 individuals with normal lung function at baseline were followed for 25 years. The incidence of COPD among nonsmokers was very low (1% COPD GLOD Stage II or more). In comparison, it was 27% of similar GOLD stage COPD in continuous smokers.^[11] The multicenter international burden of obstructive lung disease study showed that the prevalence of nonsmoker \geq II GLOD stage COPD was 5.6%. The prevalence of severe (GOLD Stage III) and very severe (GOLD Stage IV) airway obstruction was significantly lower in nonsmokers (5.9% vs. 14.1%,

$P = 0.001$). Increased age, a prior diagnosis of asthma and among women, lower education levels were associated with an increased risk for COPD among nonsmokers.^[12] Obstructive lung disease in Northern Sweden study, a population-based survey of 10,040 adults aged 20–77 in Norrbotten county in Sweden showed that the prevalence of nonsmoker \geq GLOD Stage II COPD was 3.5% with an overall prevalence of 7% among nonsmokers. Increasing age, a previous diagnosis of asthma and family history of obstructive airway disease were significant risk factors for nonsmoker COPD.^[13]

Prevalence, risk factors, and other features of nonsmoker COPD in western hemisphere may be different than other parts of the world. This issue of Lung India contains an article on nonsmoker COPD. This observational institution-based cross-sectional study from Allahabad city of India included 200 COPD patients.^[14] The proportion of nonsmoker patients was 56.5%. The most important and statistically significant risk factor for nonsmoker COPD was exposure to biomass smoke in 53.9% of patients. Other significant risk factors were treated pulmonary tuberculosis (PTB) in 32.7%, and long-standing asthma in 14.2%. Other risk factors present in about 10% of patients were occupational exposure, exposure to outdoor air pollution, and lower respiratory tract infection during childhood. It was also found that as the number of risk factors in nonsmoker COPD patients increased, mean age for detection of COPD decreased.

Biomass smoke exposure and treated PTB are important contributors to nonsmoker COPD outside western world especially in countries with high burden of tuberculosis and use of biomass fuel for cooking. We have seen above that pathogenetically biomass-related COPD may be same as smoker COPD. Moreover, smoking may coexist with biomass fuel exposure. A study on coke oven workers and in Southern China showed that the risk of COPD in those with the highest cumulative exposure to coke oven exposure and cigarette smoking was 58-fold as compared to nonsmokers not exposed to coke oven. While the risk of COPD was only 5.8-fold in coke oven exposed versus not exposed to coke oven.^[15]

Tuberculosis may affect the development of COPD in a variety of ways due to the occurrence of permanent scarring, bronchiectasis, and fibrosis. A systematic review and meta-analysis showed a three-time increased risk for COPD in patients with a history of tuberculosis. The association was strongest in people who never smoked, were <40 years of age and those living in countries with high incidence of tuberculosis.^[16] A recent prospective, nested case-control study was conducted on new cases of PTB with initial restrictive respiratory function impairment and treated according to the directly observed treatment short course strategy in Nis city of Serbia.^[17] The initial radiological extent of PTB and sputum conversion rate on culture were the most significant predictors for the

risk of PTB-associated airflow obstruction. PTB-associated airflow obstruction occurs later, during the reparative processes in active PTB and initial spirometry may be normal or show restriction during treatment phase.

Therefore, there is a continuous need for research into group of nonsmoker COPD and due emphasis should be given in current guidelines on diagnosis and management of this group of COPD. Regional researchers should specifically address their most prevalent obstructive airway disease groups rather than recruiting only smoker COPD. Tuberculosis and biomass exposure are very important risk factors for nonsmoker COPD in India. Therefore, nonsmoker COPD requires more attention in country like India where a lot of smoke is present inside and outside a home.

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